REMARKS

Claims 1-16 were pending and have been subjected to a restriction requirement and species election. Applicants' election of the Group I claims and the species are addressed above.

By this amendment, claims 5-7 are amended and 17-19 are added. Claims 10-16 are cancelled due to the restriction requirement. Claim 17 is derived from splitting claim 5 into two claims to remove the "preferably" language. Claims 6 and 7 are amended to correct the dependency to depend from claim 17. New claim 18 is supported in the specification, e.g., on page 10 at lines 12-15 and page 14 at lines 5-7. Claim 19 is supported in the specification on page 9 at lines 3-4 and page 19 at lines 10-14. Upon entry of this amendment, claims 1-9 and 17-19 will be pending.

The specification has been amended to correct publication dates and other typographical errors within the citations. No new matter has been added and entry of the foregoing amendments is respectfully requested.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned "**Version with markings to show changes made.**"

In the unlikely event that the transmittal letter is separated from this document and the U.S. Patent Office determines that an extension and/or other relief is required, Applicants petition for any required relief including extensions of time and authorize the Director to charge the cost of such petitions and/or other fees due in connection with the filing of this document to our Deposit Account No. 07-0630.

Respectfully submitted,
GENENTECH, INC.

Date: May 8, 2002

By: _____
Lee K. Tan, Ph.D.
Reg. No. 39,447
Phone: (650)225-4462

Doc # 105325

VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the specification:

Paragraphs at page 2, lines 6-25, have been amended as follows:

Polyclonal murine antibodies to TNF are disclosed by Cerami et al. (EPO Patent Publication 0212489 B1, ~~Mar. 4, 1987~~ November 30, 1994). Such antibodies were said to be useful in diagnostic immunoassays and in therapy of shock in bacterial infections. Rubin et al. (EPO Patent Publication 0218868 A3, Apr. 22, 1987) discloses murine monoclonal antibodies to human TNF, the hybidomas secreting such antibodies, methods of producing such murine antibodies, and the use of such murine antibodies in immunoassay of TNF.

Yone et al. (EPO Patent Publication 0288088 B1, ~~Oct. 26, 1988~~ Mar. 9, 1994) disclose anti-TNF murine antibodies, including mAbs, and their utility in immunoassay diagnosis of pathologies, in particular Kawasaki's pathology and bacterial infection. The body fluids of patients with Kawasaki's pathology (infantile acute febrile mucocutaneous lymph node syndrome; Kawasaki, Allergy 16:178 (1967); Kawasaki, Shonica (Pediatrics) 26:935 (1985)) were said to contain elevated TNF levels which were related to progress of the pathology (Yone et al., infra).

Other investigators have described rodent or murine mAbs specific for recombinant human TNF which had neutralizing activity in vitro (Liang, et al., (Biochem. Biophys. Res. Comm. 137:847-854 (1986); Meager, et al., Hybridoma 6:305-311 (1987); Fendly et al., Hybridoma 6:359-369 (1987); Bringman, et al., Hybridoma 6:489-507 (1987); Hirai, et al., J. Immunol. Meth. 96:57-62 (1987); Moller, et al., ~~(~~Cytokine 2:162-169 (1990)). Some of these mAbs were used to map epitopes of human TNF and develop enzyme immunoassays (Fendly et al., infra). However, these studies do not provide a basis for producing TNF neutralizing antibodies that can be used for in vivo diagnostic or therapeutic uses in humans, due to immunogenicity, lack of specificity and/or pharmaceutical suitability.

Paragraphs at page 3, lines 14-35 have been amended as follows:

Aderka, et al., Isrl. J. Med. Sci. 28:126-130 (1992) discloses soluble forms of TNF receptors (sTNF-Rs) which specifically bind TNF and thus can compete with cell surface TNF receptors to bind TNF (Seckinger, et al., J. Exp. Med. 167:1511-1516 (1988); Engelmann, et al., J. Biol. Chem. 264:11974-11980 (1989)). The cloning and expression of human 55 kd TNF receptor and soluble forms of the receptor have been described (Loetscher, et al., Apr. 20, 1990, Cell 61:351-359; Schall et al , Apr. 20, 1990, Cell 61:361-370; Nophar, et al., EMBO J. 9(10):3269-3278 (1990). Engelmann, et al., J. Biol. Chem. 265(3):1531-1536 (1990), discloses TNF-binding proteins. EP 0 433 900 ~~A1~~ B1 discloses TNF binding protein I (TBP-I), derivatives and analogs thereof, expression of a DNA encoding the entire

human type I TNF receptor, or a soluble domain thereof. WO 92/13095 discloses methods for treating tumor necrosis factor mediated diseases by administration of a therapeutically effective amount of a TNF inhibitor selected from a 30 kDa TNF inhibitor and a 40 kDa TNF inhibitor.

EP 0 526 905 discloses multimers of the soluble forms of TNF receptors, which include portions of the hp55 TNF-receptor, produced by either chemical or recombinant methods which are useful for protecting mammals from the deleterious effects of TNF. WO 92/07076 discloses modified human TNF-α receptor which consists of the first three cysteine-rich subdomains but lacks the fourth Cysteine-rich subdomain of the extracellular binding domain of the 55 kDa or 75 kDa TNF receptor for human TNF-α, or an amino acid sequence having a homology of 90% or more with the TNF receptor sequences. EP 0 412 486 ~~A1~~ B1 discloses antibodies to TNF binding protein I (TBP-I), and fragments thereof, which can be used as diagnostic assays or pharmaceutical agents, either inhibiting or mimicking the effects of TNF on cells. EP 0 398 327 ~~A1~~ B1 discloses TNF binding protein (TBP) isolated and purified having inhibitory activity on the cytotoxic effect of TNF, as well as TNF binding protein II and monoclonal antibodies thereto. EP 0 308 378 ~~A2~~ B1 discloses TNF inhibitory protein and functional derivatives used to antagonize the deleterious effects of TNF.

Paragraph at page 4, lines 1-26 has been amended as follows:

Using antibodies that interfere with LFA-1/ICAM interactions decreases or inhibits the inflammatory process by blocking the activation of T-cells and/or the extravasation of leukocytes. *In vitro*, monoclonal antibodies against LFA-1 or its ligands have inhibited T-cell activation (Kuypers, T. and Roos, D., 1989, Research in Immunology, 140:461-86; Springer, TA, 1987, Annual Rev Immunology, 5:223-52), T-cell dependent B-cell proliferation (Fischer, A. et al., 1986, J Immunol, 136:3198-203), target cell lysis (Krensky, A. et al., 1983, J Immunol, 131:~~6711-66~~11-616), and adhesion of T-cells to vascular endothelium (Dustin, ML. et al., 1988, Journal of Cell Biology, 107:321-31). The use of an anti-CD11a antibody to treat psoriasis has been described in WO 0056363. In mice, anti-CD11a antibodies have induced tolerance to protein antigens (Benjamin, R. et al, 1988, European Journal of Immunology, 18:1079-88; Tanaka, Y. et al , 1995, European Journal of Immunology, 25:1555-8), delayed the onset and reduced the severity of experimental autoimmune encephalomyelitis (Gordon, EJ et al., 1995, Journal of Neuroimmunology, 62:153-60), inhibited lupus-associated autoantibody production, and prolonged survival of several types of tissue grafts (Cavazzana-Calco MS, Sarnacki S, Haddad E, et al., Transplantation 1995;59(11):1576-82; Nakakura EK, McCabe SM, Zheng B, Shorthouse RA, et al., Transplantation 1993;55(2):412-7; Connolly MK, Kitchens EA, Chan B, et al, Clinical Immunology and Immunopathology 1994;72(2):198-203; He Y, Mellon J, Apte R, Niederkorn J., Investigative

Ophthalmology and Visual Science 1994;35(8):3218-25, Isobe M, Yagita H, Okumura K, Ihara A., Science 1992;255:1125-7; Kato Y, Yamataka A, Yagita H, et al., Ann Surg 1996;223(1):94-100; Nishihara M, Gotoh M, Fukuzaki T, et al., Transplantation Proceedings 1995;27(1):372; Talento A, Nguyen M, Blake T, et al, Transplantation 1993;55(2).418-22; van Dijken PJ, Ghayur T, Mauch P, et al., Transplantation 1990;49(5):882-6). In human clinical studies, murine anti-CD11a monoclonal antibodies have been shown to help prevent graft failure following bone marrow transplantation (Cavazzana-Calco MS, Bordigoni P, Michel G, et al., British Journal of Haematology 1996;93:131-8; Fischer A, Friedrich W, Fasth A., Blood 1991;77(2):249-56; Stoppa AM, Maraninchi D, Blaise D, Viens P, *et al.*, Transplant International 1991;4:3-7) and renal transplantation (Hourmant M, Le Mauff B, Le Meur Y, *et al.*, Transplantation 1994;58(3):377-80; Hourmant M, Bedrossian J, Durand D, *et al.*, Transplantation 1996;62(11):1565-70; Le Mauff B, Hourmant M, Rougier JP, *et al.*, Transplantation 1991;52(2):291-6).

The paragraph at page 6, lines 11-21 has been amended as follows:

Several combination therapies have been described for treating RA. The combination of etanercept (TNFR:Fc fusion protein) and methotrexate (MTX) was used to treat persistently active RA and found to provide greater clinical benefit than methotrexate alone (Weinblatt et al., Jan. 28, 1999, NEJM 340 (4): 253-259). In another clinical trial, the anti-TNF-α chimeric mouse-human antibody, cA2 (infliximab, Remicade,) was given in combination with low-dose methotrexate to RA patients (~~Mani~~ Maini et al, 1998, Arthritis & Rheumatism 41(9): 1552-1563). Anti-CD4 mAb was found to prevent collagen-induced arthritis if administered before the onset of clinical disease in the CIA mouse model but was ineffective in treating established disease. Co-administration of anti-CD4 antibody with anti-TNF α/β antibody caused significantly greater reduction in paw swelling and joint erosion than that observed by optimal anti-TNF alone (Williams et al. 1994, PNAS 91: 2762-2766). For other references on combination therapies see Kremer (1998), Arthritis & Rheumatism 41: 1548-1551 and Williams (1998), Springer Semin. Immunopathol. 20:165-180.

The paragraph at page 15, lines 29-33 has been amended as follows:

Examples of anti-CD18 antibodies include MHM23 [Hildreth *et al.*, *supra*], M18/2 (IgG2a) [~~Sanchez-Madrid~~ Sanchez-Madrid *et al*, J Exp. Med., 158: 586 (1983)], H52 [Fekete *et al.*, J. Clin Lab Immunol., 31: 145-149 (1990)], Mas191c [Vermot Desroches *et al.*, *supra*], IOT18 [Vermot Desroches *et al*, *supra*], 60.3 [Taylor *et al.*, Clin. Exp. Immunol., 71: 324-328 (1988)], and 60.1 [Campana *et al.*, Eur. J. Immunol, 16: 537-542 (1986)]. See also US 5,997,867.

The paragraphs at page 16, lines 14-33 are amended as follows:

Molecular cloning has demonstrated the existence of two distinct types of TNF receptors (TNFR) with apparent molecular masses of 55kD (type 1) (Schall et al., (1990) Cell 61:361) and 75 kD (type 2) (Smith et al., (1990) Science 248:1019), each of which naturally binds to both TNF-α and TNF-β (Loetscher et al., (1990) Cell, 61:351; Shall et al. (1990) Cell, 61:361; Kohno et al., 1990) Proc. Natl. Acad. Sci. USA 87:8331). The extracellular portions of both receptors are found naturally as soluble TNF binding proteins (Kohno et al., supra). TNF antagonists have been created which block the deleterious effect of TNF in various immune and inflammatory events (Peppel et al., (1991) J. Exp. Med., 174:1483-1489; Ulich (1993) Am. J. Path., 142:1335-1338; Howard, O.M.Z., (1993) Proc. Natl. Acad. Sci. USA 90:2335-2339; Wooley, P.H., (1993) J. Immunol. 151:6602-6607). One such antagonist (Werner et al., (1991) J. Cell. Biochem. Abstracts, 20th annual meeting, p. 115) combines the extracellular domain of human 55 kD type 1 TNFR with a portion of the hinge and Fc regions of human immunoglobulin G1 heavy chain. Another such antagonist (Mohler et al., (1993) J. Immunol. 151:1548-1561) combines the extracellular domain of human 75 kD type 2 TNFR with a portion of the hinge and Fc regions of human immunoglobulin G1 heavy chain. U.S. patents ~~5,482,130~~ 5,428,130 and 5,514,582 describe these molecules. Any of these molecules may be used as the TNF-α antagonist of the invention.

Other examples of TNF-α antagonists include the anti-TNF-α antibodies disclosed in US 5,795,967; WO 97/29131 (which discloses recombinant human antibodies and antibodies produced using phage display techniques); US 5,654,407 and US 5,994,510 (which disclose human anti-TNF-α antibodies); WO 92/11383 and WO 92/16553 (which disclose chimeric, including humanized, antibodies); US 5,656,272, US 5,919,452 and US 5,698,195 (which disclose chimeric antibodies); and ~~Fendley~~ Fendly et al, 1987, Hybridoma 6:359 and Bringman et al, 1987, Hybridoma 6.489 (which disclose additional anti-TNF-α antibodies).

In the claims

Claims 5-7 have been amended as follows:

5. (Amended) The method of any one of claims 1-4, wherein the LFA-1 antagonist is an anti-LFA-1 antibody [, preferably an anti-CD11a antibody].

6. (Amended) The method of [one of claims 1-5] claim 17, wherein the [LFA-1 antagonist] anti-CD11a antibody is a non T-cell depleting [anti-CD11a] antibody.

7. (Amended) The method of any one of claims 1-6 and 17, wherein the TNF-α antagonist is an immunoadhesin.

Claims 10-16 have been cancelled.

APPENDIX OF PENDING CLAIMS AS AMENDED ON MAY 8, 2002

1. A method of treating an LFA-1 or a TNF-α mediated disorder, comprising administering to a mammal in need thereof effective amounts of an LFA-1 antagonist and a TNF-α antagonist.

2. A method of treating cartilage damage from injury or preventing initial or continued damage by a degenerative cartilagenous disorder or injury, comprising contacting the cartilage with effective amounts of an LFA-1 antagonist and a TNF-α antagonist.

3. The method of claim 1 or 2, wherein the disorder is a degenerative cartilagenous disorder.

4. The method of claim 3, wherein the degenerative cartilagenous disorder is selected from the group consisting of rheumatoid arthritis and osteoarthritis.

5. (Amended) The method of any one of claims 1-4, wherein the LFA-1 antagonist is an anti-LFA-1 antibody.

6. (Amended) The method of claim 17, wherein the anti-CD11a antibody is a non T-cell depleting antibody.

7. (Amended) The method of any one of claims 1-6 and 17, wherein the TNF-α antagonist is an immunoadhesin.

8. The method of one of claim 7 wherein the immunoadhesin is a fusion of at least a portion of a TNF-α binding protein and a portion of an immunoglobulin

9. The method of one of claim 8, wherein the TNF-α binding protein is a TNF-α receptor - IgG Fc fusion protein.

17. The method of claim 5, wherein the anti-LFA-1 antibody is an anti-CD11a antibody.

18. The method of claim 10, wherein the fusion protein consists of the extracellular ligand binding portion of human tumor necrosis factor receptor linked to the hinge region, CH2 domain, and CH3 domain of human IgG1.

19. The method of claim 4, further comprising administering to the mammal an effective amount of methotrexate.